

Long-Term Gender-Based Outcomes for Atazanavir/Ritonavir (ATV/r)-Containing Regimens in Treatment-Experienced Patients with HIV

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Abstract: Clinical data on antiretroviral effectiveness in women are limited, especially long-term data, because women are usually underrepresented in clinical trials. This sub-analysis of a large European non-comparative, retrospective, observational cohort study evaluated gender differences in long-term outcomes in antiretroviral-experienced adult patients with HIV-1 infection switched to an ATV/r-based regimen between October 2004 and March 2007. Data were extracted from 3 European HIV databases every 6 months (maximum follow-up 5 years). Time to virological failure (VF), defined as two consecutive HIV-1 RNA ≥ 50 c/mL or one HIV-1 RNA ≥ 50 c/mL followed by treatment discontinuation (TD), and time to TD were analyzed using the Kaplan-Meier method. Associations of gender with VF and TD were analyzed using multivariate Cox proportional models. Safety and tolerability were evaluated. In total, 1294 patients (336 women, 958 men) were analyzed. No gender differences in time to VF were observed; at 3 years, the probability of not having VF was 0.59 (95%CI: 0.52, 0.65) and 0.63 (95%CI: 0.59, 0.67) for women and men, respectively. In multivariate analyses, women had a higher risk of TD than men (hazard ratio [HR], 1.54; 95%CI: 1.28, 1.85) but no increased risk of VF (HR, 1.06; 95%CI: 0.85, 1.33). Safety and tolerability were comparable between genders. In a clinical setting, long-term efficacy and safety outcomes of ATV/r-based regimens were similar by gender. Women had a higher risk of TD but no increased risk of VF. ATV/r is an effective and well-tolerated therapeutic option for treatment-experienced men and women with HIV-1 infection.

Keywords: Antiretroviral therapy, atazanavir, cohort study, gender, HIV infection, women.

INTRODUCTION

Increasing numbers of women are being diagnosed with HIV infection worldwide and women account for about one third of these new diagnoses, most of which are in women of childbearing age. For example, in 2000, in the WHO European Region, rates of newly diagnosed individuals per 100,000 were 2.6 for women and 5.8 for men, with women representing 32.1% of these new diagnoses [1]. By 2010 the corresponding values were 10.1, 16.7 and 38.0%, respectively [2]. These trends were particularly evident in Eastern Europe, where heterosexual transmission is now the most common mode of transmission [2], a trend that is also observed globally and especially in Africa [3].

Despite women representing 50% of people living with HIV globally [4], data specifically evaluating gender-based outcomes with combined antiretroviral therapy (cART) are limited. Women are systematically underrepresented in randomized clinical trials (RCTs) for a variety of reasons, such as pregnancy, or the need to adhere to complex

contraceptive regimens to avoid pregnancy, or competitive recruitment practices that may discourage the selection of women who face more complex challenges for clinical trial participation [5]. From 2000-2008 it has been estimated that the average proportion of women participating in RCTs ranged from 20% to 31% [6-9]; however, the proportion of women participants in some recent RCTs has fallen to as low as 10% [10,11]. Moreover, even if women are recruited in sufficient numbers, few reports have specifically evaluated gender differences, especially over a prolonged follow-up period.

While there is little evidence for gender-based differences in virological response to cART from either clinical studies [12-18], systematic reviews [19] or meta-analytic investigations [7], gender differences in safety profiles and higher discontinuation rates in women compared with men have been consistently reported [13,18-22]. Thus, there is a continuing medical need to further evaluate gender-based outcomes for antiretroviral (ARV) regimens commonly used in clinical practice, especially through long-term studies that have the potential to capture differences in virological response and safety profiles over time.

Regimens containing atazanavir, a once-daily protease inhibitor (PI), at a dose of 300 mg, in combination with low-dose ritonavir 100 mg (ATV/r), have demonstrated efficacy,

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safety and tolerability in clinical trials of up to 96 weeks in treatment-naïve [23-25] and -experienced patients [26, 27] as well as in both men and women [18]. In European guidelines, ATV/r is recommended as a preferred PI for the treatment of HIV-1 infection in adults and also in pregnant women [28]. In addition, no significant interaction between ATV/r and an oral contraceptive containing ethinyl estradiol (EE) and norgestimate has been observed provided the dose of EE is $\geq 30 \mu\text{g}$ [29, 30], suggesting that ATV/r is a suitable therapeutic option for women with HIV.

The current study, a retrospective cohort of 1294 treatment-experienced patients with HIV-1 infection switched to ATV/r and followed up for up to 5 years, was designed to evaluate the long-term clinical outcomes of ATV/r-containing regimens in a real-life clinical setting. In the overall cohort population, durable virological suppression with a good safety and tolerability profile has been demonstrated [31]. The aim of the present sub-analysis of this cohort was to specifically evaluate the effect of gender on the long-term outcomes of ATV/r-containing regimens in a clinical setting.

METHODS

Details of study methods have been previously published [31]; however, a brief description is provided as follows.

Study Design

This was a non-comparative, retrospective, observational study of ARV-experienced patients (including PI-experienced) stratified by viral load at baseline (HIV-1 RNA < 500 copies/mL or ≥ 500 copies/mL). Baseline was defined as the start date of ATV/r treatment. Data from patients who switched to an ATV/r-containing regimen between October 1st 2004 and March 31st 2007 were collected from three generic HIV databases; two multi-center databases, one based in France (Dat'AIDS) and the other in Germany (Competence Network for HIV/AIDS, KompNet) and one single-center database based in Sweden (InfCare HIV). An integrated study dataset was then generated from these three generic databases and patient data was extracted at 6-monthly intervals until 31st October 2009 (maximum follow-up period of 5 years).

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, and was consistent with the International Conference on Harmonization Good Clinical Practice Guidelines, Guidelines for Good Pharmacoepidemiology Practices and local regulatory requirements. Approval for cohort inclusion was obtained from the local ethical committees of all study centers.

Results for the primary endpoint for this study, the proportion of patients remaining on treatment over time stratified by plasma viral load at baseline (i.e. HIV-1 RNA < 500 copies/mL or ≥ 500 copies/mL at study entry), and secondary endpoints have been previously reported [31]. Here we report results of a pre-planned sub-analysis by patient gender.

Patients

Inclusion criteria were participation in a European HIV cohort, age ≥ 18 years on commencement of ATV/r therapy, ARV experience prior to starting ATV/r therapy, ATV/r therapy commenced between October 1st 2004 and March 31st 2007. Patients were excluded if they were treatment naïve or had no recorded start date for ATV/r therapy.

Outcomes for Gender Sub-Analysis

The following outcomes were evaluated: i) time to virological failure by gender, defined as two consecutive HIV-1 RNA ≥ 50 copies/mL or one HIV-1 RNA ≥ 50 copies/mL followed by treatment discontinuation for any reason, expressed as the probability of not having virological failure and estimated using the Kaplan-Meier method; ii) time to discontinuation by gender, expressed as the probability of remaining on treatment over time and estimated using the Kaplan-Meier method; iii) the proportion of patients discontinuing and the reasons for discontinuation by gender; and iv) the long-term safety profile by gender.

Statistical Analyses

For the analysis of time-to-event data, the Kaplan-Meier method was considered to be the most appropriate technique. All patients were analyzed up to the date of their last contact, including patients with ATV/r treatment interruptions, provided the duration of interruption was ≤ 90 days. Patients with missing data or who were lost to follow-up were censored.

The long-term safety profile of ATV/r treatment was evaluated by collecting data on reported adverse events (AEs) and laboratory abnormalities. AE data was collected and analyzed for all patients up to the point of ATV/r treatment discontinuation or until the end of the follow-up period.

This secondary sub-analysis by gender was not powered to detect statistically significant differences; therefore, no formal statistical significance testing was undertaken for comparisons between genders in this report.

Multivariate Cox proportional analyses were conducted to evaluate the association of patient gender with time to virological failure and time to treatment discontinuation. Analyses were adjusted for potential confounding factors including, age, mode of HIV-1 transmission, baseline HIV-1 RNA level and CD4 count, country, and ARV treatment (both in terms of duration of exposure and drug-class).

RESULTS

Patients

A total of 1294 patients were included in the study, 336 women and 958 men, and were followed up for a total of 2748 patient-years. Details of patient disposition are summarized in Fig. (1). Baseline characteristics by gender were generally similar and are presented in Table 1. However, female patients were significantly younger than male patients.

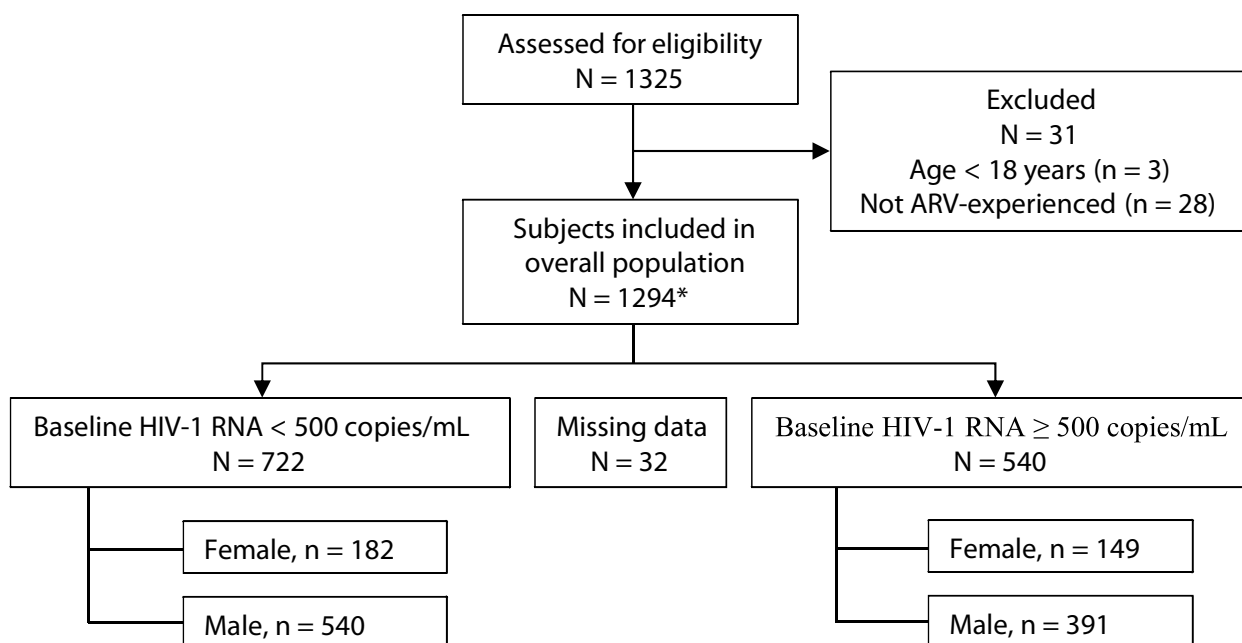


Fig. (1). Patient disposition.

Table 1. Baseline Characteristics by Gender

| | Female (n = 336) | Male (n = 958) |
|--|--------------------|--------------------|
| Age, years, median (min, max) | 40 (20, 79) | 44* (18, 85) |
| CDC Class C AIDS, n (%)† | 75 (22.3) | 197 (20.6) |
| Baseline HIV-1 RNA, copies/mL, median (min, max) | 1622 (22, 2168000) | 1260 (20, 9540000) |
| Baseline HIV-1 RNA, using 500 copies/mL cut-off‡ | | |
| < 500 copies/mL, n (%) | 182 (55.0) | 540 (58.0) |
| ≥ 500 copies/mL, n (%) | 149 (45.0) | 391 (42.0) |
| Baseline HIV-1 RNA, using 50 copies/mL cut-off§ | | |
| < 50 copies/mL, n (%) | 113 (37.2) | 300 (36.3) |
| ≥ 50 copies/mL, n (%) | 191 (62.8) | 526 (63.7) |
| CD4 count, cells/μL, median (min, max) | 359 (5, 1373) | 373 (1, 1629) |
| CD4+ <50 cells/μL, n (%) | 13 (3.9) | 31 (3.2) |
| Prior ARV exposure, years, mean (SD) | 5.6 (4.1) | 5.8 (3.9) |
| Prior PI exposure, years, mean (SD) | 3.3 (2.6) | 3.6 (2.9) |

*P < 0.001. Data available for †941, ‡1262, and §1130 patients. CDC, Centers for Disease Control; PI, protease inhibitor.

Outcomes

Discontinuation by Gender

Of the 958 male patients enrolled, 383 (40.0%) discontinued ATV/r-containing therapy compared with 175 of the 336 (52.1%) female patients. After 3 years of follow-up, the probability of remaining on an ATV/r-containing regimen was lower for female patients (0.46; 95% CI: 0.40, 0.52) than for male patients (0.58; 95% CI: 0.54, 0.61) (Fig. 2A, Kaplan-Meier analysis). The median time to discontinuation was estimated to be 33 months (95% CI: 29, 44) in female patients and 48 months (95% CI: 45, not

calculable) in male patients. In adjusted multivariate Cox analyses, female gender was associated with an increased risk of ATV/r treatment discontinuation (Hazard Ratio 1.54; 95% CI: 1.28, 1.85; P < 0.001).

The principal known reasons for discontinuation were AEs, patient decision and lack of efficacy in both female and male patients, although these proportions were slightly higher for female patients (Table 2). Lack of efficacy was defined as treatment failure (clinical, virological or immunological), resistance, drug interaction, or other therapeutic reasons. Pregnancy was a reason for discontinuation in 2.4% of female patients.

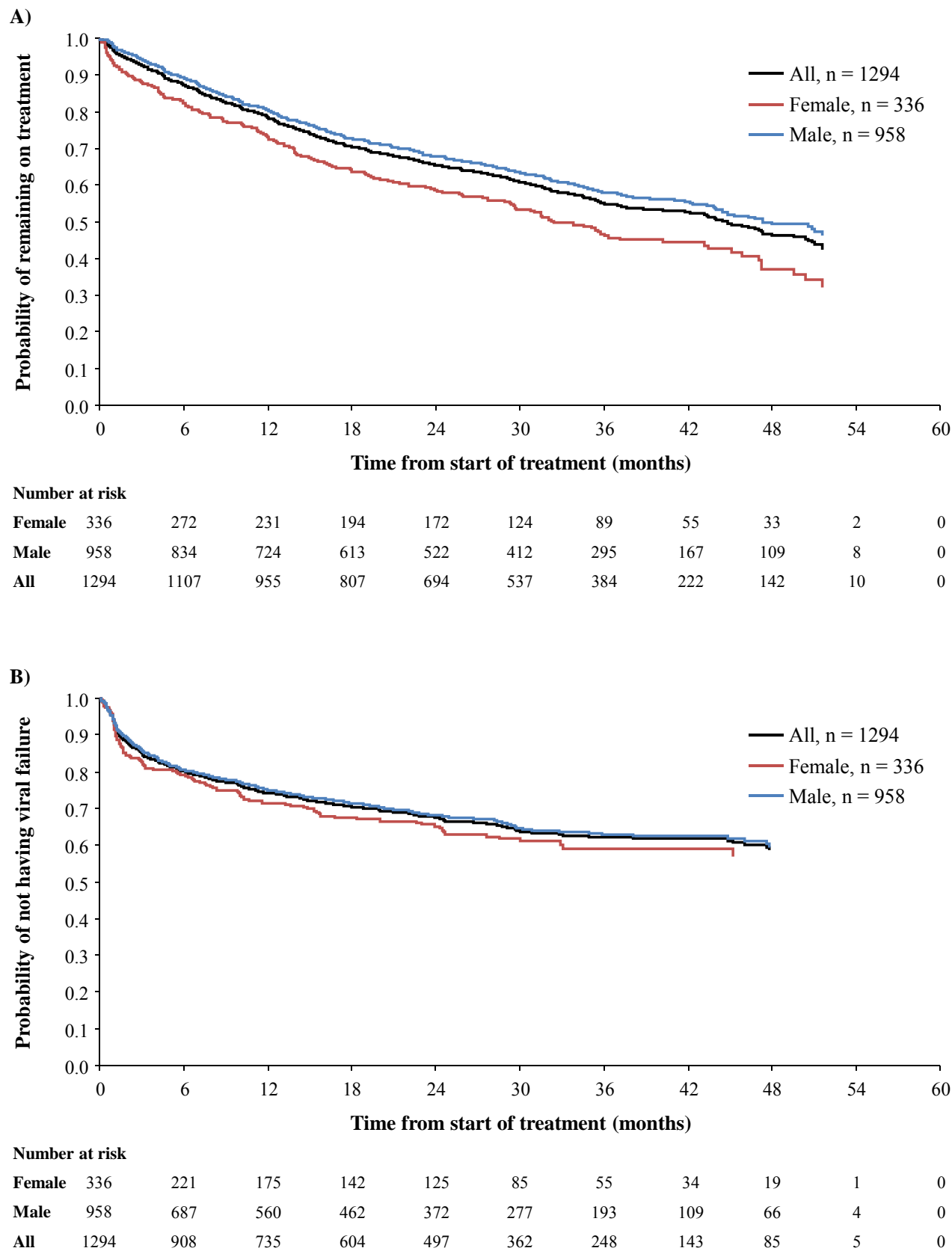


Fig. (2). Kaplan-Meier survival function by gender: **A)** time to discontinuation; and **B)** time to virological failure.

Table 2. Reasons for Discontinuation by Gender

| | Female (n = 336) | Male (n = 958) |
|--|------------------|----------------|
| Discontinued ATV/r, n (%) | 175 (52.1) | 383 (40.0) |
| Reason for discontinuation, n (%) [*] | | |
| Adverse event | 47 (14.0) | 91 (9.5) |
| Lack of efficacy [†] | 22 (6.5) | 40 (4.2) |
| Death | 4 (1.2) | 16 (1.7) |
| Patient decision | 26 (7.7) | 46 (4.8) |
| Pregnancy | 8 (2.4) | NA |
| Poor/non compliance | 3 (0.9) | 2 (0.2) |
| Other [‡] | 26 (7.7) | 49 (5.1) |
| Unknown [§] | 39 (11.6) | 139 (14.5) |

^{*}Only one reason for discontinued was allowed for each patient. [†]Includes "Treatment failure (clinical, virological or immunological), Resistance, Drug interaction, Other therapeutic reasons". [‡]Includes "Other reason, End of treatment, Simplification, Start protocol, End protocol, Structured treatment interruption, Alternative therapy, Other reasons, Drug abuse, Other treatment, Impairment of quality of life, Dose adjustment". [§]Discontinuation but reason unknown. NA, Not applicable.

Virological Response by Gender

After 3 years of follow-up, the probability of not having virological failure on an ATV/r-containing regimen was comparable in female (0.59; 95% CI: 0.52, 0.65) and male patients (0.63; 95% CI: 0.59, 0.67) (Fig. 2B, Kaplan-Meier analysis). In adjusted multivariate Cox analyses, female gender was not associated with a higher risk of virological failure (Hazard Ratio 1.06; 95% CI: 0.85, 1.33; P = 0.612).

Adverse Events by Gender

AEs, regardless of causality, are presented in Table 3. The overall proportion of patients reporting AEs was comparable between female (45.5%) and male patients (49.7%); however, some gender-based differences were observed for specific AEs. Diarrhea and grade 3-4 lipid abnormalities were observed less frequently in women than in men, and clinical acquired lipodystrophy was observed more frequently in women than in men (Table 3). No gender-based differences were noted in rates of AEs of nausea or jaundice, or in rates of Grade 3-4 hyperbilirubinemia or serum creatinine (Table 3).

DISCUSSION

This cohort study, examining treatment-experienced patients switched to an ATV/r-containing regimen in a real-life clinical setting, revealed no overall gender differences in efficacy and safety after follow-up for up to 5 years.

Women are often underrepresented in RCTs. As a result, determining gender differences is not always possible because gender analyses are often not pre-planned and/or lack statistical power. Analyses of differences in virological response are further complicated by the use of composite endpoints that combine assessments of efficacy, safety and/or tolerability in some studies, in which differences in safety or tolerability could explain observed gender differences in virological response. Overall results from a

large meta-analysis including 20, 328 HIV-positive patients from 40 RCTs examining gender-based differences in efficacy, defined as achieving an HIV-1 RNA level of < 50 copies/mL, did not demonstrate statistically significant differences in overall week-48 outcomes; however, better treatment responses for males compared with females were identified in sub-group analyses for treatment-naïve Caucasian and treatment-experienced North American patients [7].

Table 3. Selected Adverse Events (Regardless of Causality) by Gender

| | Female (n = 336) | Male (n = 958) |
|--|------------------|----------------|
| Total clinical AEs (any grade), n (%) | 153 (45.5) | 476 (49.7) |
| Selected AEs of interest (any grade), n % | | |
| Nausea | 2 (0.6) | 5 (0.5) |
| Diarrhea | 5 (1.5) | 47 (4.9) |
| Jaundice | 3 (0.9) | 4 (0.4) |
| Lipodystrophy, acquired | 16 (4.8) | 25 (2.6) |
| Nephrolithiasis | 1 (0.3) | 6 (0.6) |
| Bone density abnormality | 1 (0.3) | 0 |
| Selected laboratory AEs (Grade 3-4)*, n/N [‡] (%) | | |
| Total cholesterol (≥ 300 mg/dL) | 10/213 (4.7) | 50/711 (7.0) |
| Triglycerides (≥ 751 mg/dL) | 1/213 (0.5) | 36/706 (5.1) |
| LDL-cholesterol (≥ 190 mg/dL) | 10/148 (6.8) | 47/521 (9.0) |
| Total bilirubin elevation (> 2.5 x ULN) | 132/230 (57.4) | 441/709 (62.2) |
| Creatinine (> 2 x ULN) | 5/173 (2.9) | 8/371 (2.2) |

*Toxicity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. [†]Patients with at least one laboratory value above thresholds whilst on treatment. [‡]Patients with laboratory parameter values while on treatment. ULN, upper limit of normal.

Studies evaluating gender differences for specific ARVs, especially in experienced patients are scarce. In a non-comparative study of ritonavir-boosted darunavir (DRV/r), the GRACE study, non-significant gender differences in virological response were observed [13]. Although this study represented an interesting attempt to proactively assess treatment outcomes in women, it was limited by the short duration of follow-up (48 weeks) and the fact that results obtained from a study population with a high proportion of African-American women may not be comparable to other populations, for example, those in Europe [13].

Cohort studies afford the opportunity of evaluating outcomes in real-life clinical settings, with a larger number of patients over longer periods of follow-up, and thus provide valuable complementary information to that obtained from clinical trials. In the analysis presented here, no differences in efficacy by gender were observed. Information on racial origin was only available for the German cohort (90% Caucasian), but as Caucasian classification is 88% in the largest European cohort study (EuroSIDA) [32], these results can be considered to be clinically relevant to the European population.

The results presented here provide additional information on the use of ATV/r-based regimens in women. Previous results from sub-analyses of ATV/r clinical trials in ARV-naïve patients have shown different results [18, 33]. In the CASTLE study (31% of women at baseline), lower rates of confirmed virological response at 96 weeks to ATV/r or ritonavir-boosted lopinavir (LPV/r) were observed among women compared with men, but no gender difference was apparent in supportive analyses that used a definition of virological response based upon observed cases [18]. The AIDS Clinical Trial Group (ACTG) A5052 study (17% of women at baseline), suggested that women receiving ATV/r were at higher risk of virological failure at 96 weeks compared with men [33], although the general risk of virological failure was low regardless of treatment arm or gender [25].

Female sex has been also associated with high risk of virological failure at 96 weeks in the ACTG 5142 study (20% of women at baseline), which compared 3 class-sparing regimens, efavirenz (EFV) plus two nucleoside reverse transcriptase inhibitors (NRTIs) vs LPV/r plus two NRTIs vs LPV/r plus EFV, in treatment-naïve HIV-1 infected patients [34]. However, no comparative data by treatment arm were available for this study. Similarly in a pooled analysis of the ECHO and THRIVE clinical trials (overall, 24% of women at baseline), which compared rilpivirine (RPV) vs EFV in ARV-naïve HIV-1 infected patients, the proportion of patients achieving a virological response at 48 weeks was similar in both women and men and across treatment arms, although the proportion of patients with virological failure was higher in women treated with RPV [12].

These findings illustrate the paucity of clinical trials that are statistically powered to detect outcome differences by gender [35]. In addition, the use of composite endpoints in some of these studies makes it difficult to interpret potential gender differences in efficacy as they may be confounded by differences in discontinuation rates due to safety and/or tolerability issues [13,14, 36, 37]. In the present cohort, after adjusting for potential confounding factors, female sex was associated with a higher risk of discontinuation but not with a higher risk of virological failure, suggesting that factors other than virological failure have driven the higher rate of discontinuation observed in women.

Increased rates of treatment discontinuation in women compared with men have been consistently reported in studies exploring gender differences to ARVs [13, 18, 22]. As noted, the increased rate of discontinuation in female patients observed in the current cohort appeared to be driven by reasons other than virological failure. Higher proportions of women reported discontinuations due to AEs and patient choice. Pregnancy was given as a reason for discontinuation in 2.4% of women. However, reasons for discontinuation were unknown in 11.6% of women and in 14.5% of men, which, although not unexpected in a cohort study, indicates the need for further investigations to better characterize the reasons for gender-based differences in discontinuation rates. It is possible that women planning for pregnancy may have accounted for some of these unknown discontinuations because, at the time of cohort data collection, ATV/r was not

considered as a preferred agent in pregnancy as it is now according to recent European treatment guidelines [28].

It is known that female patients with HIV infection show different susceptibilities to ARV-associated AEs compared with men [20, 38]. Thus, gender-based differences in safety and tolerability might contribute to the higher discontinuation rates observed in female patients. For example, the significantly higher pharmacokinetic exposure to ritonavir in women compared with men could result in poorer tolerability to ritonavir-containing regimens in female patients [39]. In the GRACE study, discontinuation rates were higher in female (32.8%) than in male patients (23.2%) [40]. Overall AEs were balanced across genders in this study, but female patients reported more nausea and vomiting, and discontinuation rates due to AEs were higher in women, suggesting that tolerability issues may have contributed to the overall higher rates of discontinuation in female patients [13]. In the gender sub-analysis of the CASTLE study, although discontinuation rates in patients receiving ATV/r were higher in female (22%) than in male patients (15%), overall rates of adverse events were balanced with only a marginally higher rate of nausea in female (7%) compared with male (3%) patients [18]. In the current cohort, the overall safety profile was comparable between genders, with only small differences noted. These marginal differences in AEs are unlikely to have explained the increase in discontinuation amongst female patients reported in the current cohort. Indeed, emerging literature suggests that increased rates of ARV discontinuation in female patients can occur for many reasons that may be dependent not only upon treatment-related tolerability factors, but also upon ethnic and psychosocial factors [41]. Limitations in data collection often do not allow for detailed analyses of the reasons for treatment discontinuation.

Treatment discontinuation was greater for women, as noted in the previous analysis of the current cohort [31]; however, overall rates of discontinuation up to 5 years were favorable when compared with other cohort studies examining discontinuation rates with several different ARV regimens [21, 42]. The convenience of once-daily administration with ATV/r consequently reducing pill burden and the overall good safety and tolerability profile of ATV/r may have contributed to these favorable rates of discontinuation in both women and men.

Owing to the retrospective, cohort design of this study, a number of limitations must be considered. First, this represents a *post hoc* subgroup analysis of the original cohort and, therefore, is not adequately powered to detect differences. Second, bias from missing data or patients lost to follow-up cannot be excluded. Third, in contrast to RCTs where all AEs are systematically reported and assessed for causality, in real-life cohort studies AEs may not be routinely reported and causality is difficult to establish. However, AEs reported in the context of long-term cohort studies may be more representative of clinical practice and, therefore, provide additional clinically relevant information complementary to that obtained from clinical trials. Finally, information on genotypic resistance was not available for this study. Despite these limitations, study strengths were the inclusion of a large number of patients from different European countries, including more women (26%) than are

usually enrolled in RCTs, who were followed up over an extended period. In addition, well-designed cohort studies provide an important opportunity to evaluate populations usually underrepresented in RCTs and thus provide complementary information on patients who would otherwise have been ineligible for participation in RCTs [43].

CONCLUSION

In this real-life ARV-experienced cohort over a follow-up period of up to 5 years, ATV/r-containing regimens demonstrated durable virological suppression irrespective of gender, and showed an overall long-term safety profile that was comparable between genders and consistent with that previously observed in clinical trials. Although the rate of ATV/r treatment discontinuation was higher in women than in men, this was driven by reasons other than virological failure. In addition, higher discontinuation rates in female patients have been consistently observed across a wide range of ARV regimens. Moreover, in the previous analysis of this cohort, overall rates of discontinuation up to 5 years were favorable when compared with other cohort studies examining discontinuation rates with several different ARV-regimens. Thus, ATV/r can be considered an effective and well-tolerated therapeutic option for treatment-experienced female and male patients with HIV-1 infection.

CONFLICT OF INTEREST

VS-J has served on advisory boards and/or speakers' bureaus and has received honoraria or consulting fees from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Roche. PP has received honoraria for advisory board membership from Bristol-Myers Squibb, Gilead, and Merck Sharp & Dohme. NB has served on advisory boards and/or speakers' bureaus and has received honoraria or consulting fees from Abbot and Essex Pharma. AT has served on advisory boards and/or speakers' bureaus and has received honoraria or consulting fees from Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Merck Sharp & Dohme. CM is the Cohort Manager of KompNet HIV/AIDS children's cohort, which is supported in part by Bristol-Myers Squibb through an unrestricted educational grant, and has received travel support funded by Abbott. SE has served on advisory boards and/or speakers' bureaus and has received honoraria, consulting fees or research grants from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Roche, and ViiV Healthcare. MHB is an employee of Altigapharma and has provided support as Protocol Manager to this study funded by Bristol-Myers Squibb. TN and MJJ-E are employees of Bristol-Myers Squibb.

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PATIENT CONSENT

Declared none.

HUMAN/ANIMAL RIGHTS

Declared none.

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